virus, we further demonstrate that FGI-103 can protect animals from an otherwise lethal infection when used either in a prophylactic or therapeutic setting and that a 'single treatment', administered after infection, is sufficient to confer protection from lethal Ebola or Marburg virus challenge. 100% efficacy from a single, low dose treatment provides a proof-of-concept direct in vivo validation that FGI-103 in its current composition is bioavailable, efficacious and a viable lead for further therapeutic development. Exploratory in vitro antiviral testing further identified inhibitory activity against members of many different, otherwise unrelated virus families to include RSV, PIV and HBV, suggesting that perhaps FGI-103 potentially interferes with a common 'host' – target or – pathway utilized to varying extent by these different viruses. Altogether, these findings suggest FGI-103 may provide a much-needed 'broad-spectrum' opportunity to target multiple and otherwise intractable viral diseases.

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In vitro transport, activation and antiviral evaluation of new HPMPA prodrugs synthesized on a solid support

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9-[(2*S*)-3-Hydroxy-2-phosphonomethoxypropyl]adenine (HPMPA) is a broad spectrum antiviral agent that is highly potent against orthopox viruses, including cowpox, vaccinia, and variola (smallpox) virus. Unfortunately, it exhibits low oral bioavailability due to the presence of a phosphonic acid group, which is ionized at physiological pH. We report here extension of our phosphonate ester amino acid prodrug approach (*Mol. Pharm*, **2008** 5, 598) to HPMPA. One negative charge in the drug is masked by conversion to its cyclic form (cHPMPA) and the other by installation of the promoiety via esterification of the remaining POH with the side chain hydroxyl group of an appropriate single amino acid or dipeptide, containing a free N-terminal amine function and a C-terminal carboxylate alkyl ester group. A small library for SAR studies consisting of derivatives with varying C-terminal ester alkyl functions, amino acid stereochemistry, and P-O-C linkages was constructed using solid phase synthetic chemistry, including (L)-Ser(OMe)-cHPMPA, (D)-Ser(OMe)-cHPMPA, (L)-Ser(O*i*-Pr)-cHPMPA, (L)-Val-(L)-Ser(OMe) and (L)-Val-(L)-Ser(O*i*-Pr). The relative advantages of the new solid phase *vs*. conventional solution approaches to preparation of these compounds will be discussed. The stability and hydrolysis products of the compounds in tissue homogenates were evaluated by LC-MS. In intestinal homogenate, the amino acid prodrugs released cHPMPA in yields up to 90%. (L)-Ser(O*i*-Pr)-cHPMPA showed increased stability in both homogenate and phosphate buffer media compared to (L)-Ser(OMe)-cHPMPA. The dipeptide prodrugs had longer half-lives and different mechanisms of activation. The anti-viral (cowpox, vaccinia, CMV) potential of the new prodrugs will be assessed, based on data from *in vitro* assays.

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New peptidomimetic prodrugs of acyclic and cyclic cidofovir: sar studies of chemical and enzymatic activation mechanisms

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Cidofovir (HPMPC) and its similarly potent cyclic form (cHPMPC) are possible therapies for orthopox virus infections, but are limited in this role by low oral bioavailability. We have previously reported the synthesis of several dipeptide prodrugs of cHPMPC (aa-Ser-CO_2R cHPMPC) in which the amino acid stereochemistry or the peptide carboxyl R group were modified. These modifications resulted in significant differences in stability and transport properties. When the dipeptide prodrugs were investigated in phosphate buffer and tissue homogenates, both chemical and enzymatic activation pathways were observed. In the current study, a series of novel single amino acid (Ser, Thr, and Tyr) and dipeptide prodrugs of cHPMPC and HPMPC were synthesized and evaluated for their mechanism of activation and intestinal transport potential. The presence of a free N-terminal amino group in the Ser and Thr conjugates of cHPMPC catalyzes cleavage of the promoiety and releases cHPMPC in 80-90% yield, while the Tyr conjugate requires enzymatic activation. Dipeptide HPMPC conjugates, prepared from their corresponding cHPMPC analogues, show enhanced stability and require phosphatase activation. The effects of these and other structural modifications, including methylation of the dipeptide amido nitrogen [C(O)-N(CH_3)] and reversing the dipeptide sequence (Ser-Ala-CO_2R), on the activation pathways and transport potential of the compounds will be discussed, together with *in vitro* antiviral (cowpox, vaccinia, CMV) data. The results illustrate the versatile tunability of these side chain-linked peptidomimetic acyclic and cyclic cidofovir derivatives with respect to optimizing their transport and activation properties.

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